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Effect of dietary interventions in Mild Cognitive Impairment: a systematic review.

A.M McGrattan[1], C.T McEvoy[1, 2], B. McGuinness[1], M.C. McKinley[1] and J.V. Woodside[1]

[1]*Centre for Public Health, Queens University Belfast, Belfast, BT12 6BJ.*

[2] *Global Brain Health Institute, University of California San Francisco, CA & Trinity College Dublin, Dublin 2*

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Abstract

Diet has been investigated in relation to its ability to promote cognitive function. However, evidence is currently limited and has rarely been systematically reviewed, particularly in a mild cognitive impairment (MCI) population. This review examined the effect of diet on cognitive outcomes in MCI patients. A total of five databases were searched to find randomised controlled trial (RCT) studies, with diet as the main focus, in MCI participants. The primary outcome was incident dementia and/or Alzheimer's disease (AD) and secondary outcomes included cognitive function across different domains using validated neuropsychological tests. Sixteen studies met the inclusion criteria. There was a high degree of heterogeneity relating to the nature of the dietary intervention and cognitive outcomes measured, thus making study comparisons difficult. Supplementation with vitamin E (one study, n 516), Ginkgo biloba (one study, n 482) or Fortasyn Connect (one study, n 311), had no significant effect on progression from MCI to dementia and/or AD. For cognitive function, the findings showed some improvements in performance, particularly in memory, with the most consistent results shown by B vitamins, including folic acid (one study n 266), folic acid alone (one study, n 180), DHA and EPA (two studies, n 36 and n 86), DHA (one study, n 240) and flavonol supplementation (one study, n 90). The findings indicate that dietary factors may have a potential benefit for cognitive function in MCI patients. Further well-designed trials are needed, with standardised and robust measures of cognition to investigate the influence of diet on cognitive status.

Background

Cognitive impairment poses a major global public health challenge due to increasing prevalence in line with population ageing[(1)]. The transition from mild cognitive impairment (MCI) through to the various forms of dementia, such as Alzheimer's disease (AD), is one of the costliest burdens on health service delivery[(2)]. The National Institute for Aging-Alzheimer's Association (NIA-AA) developed core clinical criteria to inform the diagnosis of MCI[(3)]. This identifies that a person with MCI should display a change in cognition, expressed through personal concern or identification from a physician. Additionally, individuals should display a lower performance in at least one cognitive domain than that expected for their age and education, over a period of time. Such domains are memory, executive function, attention, visuospatial skills and language. Finally, individuals with MCI may have slight problems with complex daily tasks, however, generally live an independent lifestyle with minimal assistance[(3)]. MCI is described as a transitional stage between the expected cognitive decline of normal ageing and that of dementia[(4)]. Furthermore, it has been estimated that 46% of MCI patients develop dementia within three years from diagnosis[(5)]. Therefore, it is critical to identify effective interventions that can protect against cognitive decline in this vulnerable high risk group [(6)].

Despite pharmacological advances, there are no effective treatments to delay or reverse cognitive impairment. The inflammatory mechanisms and oxidative stress involved in the aetiology of cognitive decline and dementia[7], indicates a potential role for nutrition in its prevention[8]. Furthermore, processes such as neurogenesis and neuronal connectivity involved in the function of the brain are influenced by dietary components[9,10]. The role of nutrition in cognitive health outcomes has been examined in terms of a range of nutrients/dietary patterns, investigating the role that single nutrients, such as n-3 PUFA[7], as well as whole foods/diet interventions, such as the DASH diet[11], a ketogenic diet[12], or the Mediterranean diet[13] may have, particularly in relation to their effect on reducing inflammation and oxidative stress[14,15,16]. It has been suggested that, although investigations into single nutrients have importance from a mechanistic point of view, studies which provide whole-diet analysis acknowledge that, in everyday situations, foods are consumed in complex combinations and may be a more representative approach to measure the effect of diet on cognition[17]. Furthermore, ensuring older adults with MCI stay physically active could have beneficial effects on cognition[18,19], alongside engaging in cognitive training strategies to boost cognitive function. This involves a variety of either computerised or hand-written techniques to enhance memory, language and attention[20]. However, the available research in this area is variable, with a lack of specific studies in MCI[6].

Ultimately, there is a need for this systematic review to examine what is known to date about the role of diet on cognitive health, either independently or in conjunction with other lifestyle modifications, specifically in a MCI population. To our knowledge, the effect of dietary interventions on cognitive health outcomes, particularly in high risk populations, like MCI has not been previously systematically reviewed and therefore this has the potential to establish the evidence base for possible management strategies and also define the scope for future research, if required. Thus, the aim of this systematic review was to examine the effect of diet, either alone or in combination with lifestyle and/or cognitive strategies, on cognitive health outcomes in patients with MCI.

Methods

The methods for this systematic review were based on the Centre for Reviews and Dissemination (CRD) guidance for undertaking systematic reviews in health care[21]. To be included in this review, the article had to be a randomised controlled trial (RCT) design, conducted in patients with MCI and with diet as the main focus of the intervention. Pilot studies were excluded when a paper clearly stated that the research was a "pilot study". Interventions could focus on diet alone (a dietary pattern or dietary supplements) or in combination with lifestyle and/or cognitive strategies. An overview of the inclusion and exclusion criteria is provided in table 1. Incident dementia or AD was the primary outcome measure. Secondary outcomes included overall cognitive function or specific cognitive

domains such as memory, executive function, language, attention or visuospatial skills measured using validated neuropsychological tests for example, Mini Mental State Examination (MMSE), Cambridge Cognition Examination (CAMcog) or Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).

Study Identification

A comprehensive literature search was undertaken in June 2016 using Ovid MEDLINE, EMBASE, PsycINFO, Web of Science and Scopus. A suitable search strategy was devised considering key terms used in associated reviews relating to "diet", "lifestyle", "cognitive strategies", "cognition" and "behaviour change". Studies were restricted to English Language and similar search terms were used in each database. This detailed search strategy was developed in Ovid MEDLINE (Supplementary Material Table 1) and this strategy was tailored for the other databases. The literature search was repeated in November 2016 and March 2018 to identify new publications. The reference lists of articles and other relevant systematic reviews were screened for potential trials not identified by the electronic search.

Data Extraction

Titles and abstracts of potentially eligible studies were screened by the first author (AMG). Any articles not meeting the inclusion criteria were excluded at this stage. Full text articles were obtained for the remaining studies and the study methodology was further assessed for eligibility (AMG). Any queries with regards to inclusion of articles were discussed among the research team (CME, JW, BMG and MMK). A data extraction form was generated to summarise the key characteristics of the included articles, extracting information on participant, intervention, and methodological characteristics and cognitive outcome results. Data was extracted for the primary and secondary outcomes as stated previously. Information on quality of life and number of participants experiencing one or more serious adverse events was also extracted when provided in papers in addition to the primary and secondary outcomes mentioned. Where studies included validated biomarkers (e.g. structural MRI or amyloid imaging) secondary to cognitive outcome measures, these data were also extracted. The extraction was undertaken by the first author (AMG) and this was independently checked by the second author (CME) and both reviewers discussed any discrepancies as required.

Quality Assessment

The methodological quality of the included studies was assessed using the JADAD scale[22]. This scale has been widely used to assess the quality of RCTs included in systematic reviews with regards

to randomisation procedures, double blinding and participant withdrawals. A score of 1 was allocated for each "yes" answer to the following three questions;

(1) Was the study described as randomised?

(2) Was the study described as double blind?

(3) Was there a description of withdrawals and drop outs?

An additional score of 1 was awarded if;

(4) The randomisation process was described and appropriate

(5) The method of double blinding was described and appropriate.

The maximum possible score was 5[22].

The risk of bias was assessed using the Cochrane classification[23]. Each study was assessed for the following (where appropriate): (1) selection bias; (2) performance bias; (3) detection bias; (4) attrition bias and (5) reporting bias. Individual studies were assessed as either low, high or uncertain risk for the adequacy of the stated variables.

Data Analysis

The data collected were expected to display a high degree of heterogeneity, therefore quantitative synthesis was unsuitable. The results were summarised using narrative synthesis and presented in tables.

Results

The systematic search in June 2016 generated a total of 2130 articles (2108 through database searches and 22 through searches of reference lists). Following the removal of 650 duplicates, 1480 articles were screened for eligibility by examining their titles and abstracts. This process excluded 1447 studies and the full texts of 33 papers were obtained; 22 articles were excluded for the reasons outlined in figure 1. Following a 2nd (November 2016) and 3rd (March 2018) literature search, five further studies were identified that met the inclusion criteria and so 16 studies were included. As per the review protocol, the results have been displayed according to the primary (incident dementia or AD) and secondary (cognitive function) outcomes. For cognitive function, as per the NIA-AA criteria for the diagnosis of MCI[3], the results were grouped according to the following cognitive domains: (1) memory; (2) executive function; (3) attention; (4) language and (5) visuospatial skills, with an additional section reporting global cognitive function. When papers did not specify the cognitive domain measured, the results were grouped under "additional cognitive function measures" (supplementary material, table 2). A descriptive list of the most frequently reported cognitive function tests used in the studies is provided in the supplementary material.

Study Characteristics

An overview of the study characteristics is shown in table 2. Of the 16 studies included in analysis, 13 studies used dietary supplements or single foods as their diet intervention, including folic acid[24], Vitamin B combination (folic acid, vitamin B12 and vitamin B6)[25], Gingko Biloba[26], n-3 fatty acids (DHA+EPA[27,28,29] and DHA[30]), Vitamin E[31], Chromium supplementation[32], the medical food, Souvenaid containing the specific nutrition combination Fortasyn Connect[33], cocoa flavanols[34], Concord grape juice[35] and wild blueberry juice[36]. The three remaining studies focused their interventions on nutritional counselling in combination with healthy eating advice and calorie restriction[37], high–saturated fat/high–glycaemic index diet vs a low–saturated fat/low–glycaemic index diet[38] and a high carbohydrate vs a very low carbohydrate diet[12]. A figure detailing the included studies and their dietary exposure linked to the cognitive outcome measures assessed is provided in the supplementary material (Figure 1). One study[37] encouraged both intervention and control participants to partake in physical activity (150 minutes per week) as per World Health Organisation (WHO) recommendations[39]. There were no studies which included cognitive strategies as part of their intervention. Furthermore, two studies stated that participants had amnesic MCI (aMCI)[38] or prodromal AD[33] while all other studies reported a diagnosis of MCI.

Primary Outcome Measure – Incident Dementia and Alzheimer's disease

Three of the included studies had an outcome measure of incident dementia and/or AD[26,31,33]. Vitamin E supplementation over three years showed no significant difference in the diagnostic rate of AD in participants with MCI taking vitamin E (2000 IU) *vs* placebo (Hazard ratio (HR) 1.02, 95% CI 0.57-1.13)[31]. In the vitamin E group, 33/257 (13%) and 38/259 (15%) participants in the placebo group progressed to possible or probable AD in the first 12 months (RR 1.02, 95% CI 0.96-1.10). At 36 months, 76/257 (30%) in the vitamin E group and 73/259 (28%) in the placebo had progressed to AD (RR 1.03, 95% CI 0.79-1.35)[31]. Likewise, a USA based study with intervention follow up over 6.1 years and found no significant difference between Gingko Biloba *vs* placebo for the outcomes of all dementia (9.82/100 person-years vs 8.68/100 person-years, HR 1.13, 95% CI 0.85-1.50), AD without vascular dementia (VaD) (7.02/100 person-years vs 6.09/100 person-years, HR 1.15, 95% CI 0.83-1.61), AD with VaD (2.10/100 person-years vs 2.20/100 person years, HR 0.96, 95% CI 0.54-1.71), total AD (9.12/100 person-years vs 8.28/100 person-years, HR 1.10, 95% CI 0.83-1.47) and VaD without AD (0.18/100 person-years vs 0.30/100 person-years, HR 0.59, 95% CI 0.10-3.51)[26]. Finally, supplementation with Souvenaid (125ml/day of the specific nutrition combination Fortasyn Connect) *vs* control, showed no statistically significant difference in diagnosis of dementia at 24 months between groups (59/158 (37%) (control) *vs* 62/153 (41%) (intervention))[33].

Secondary Outcome Measure- Cognitive Function

Memory

As shown in table 3, there were 25 cognitive tests used to measure the domain of memory, and it was assessed in 15 out of the 16 studies (94%) and hence was the most tested cognitive domain. Overall, nine out of the 15 studies (53%) (B vitamin[25], DHA+EPA[27,28,29], DHA[30], vitamin E [31], cocoa flavonols[34], concord grape juice[35] and wild blueberry juice[36]) showed a significant difference between groups at study completion in at least one cognitive function test measuring memory. Fish oil supplementation (3x 430 mg DHA + 150 mg EPA daily for 12 months), produced significant improvements in visual reproduction I and RAVLT delayed recall *vs* placebo group (all $p<0.05$) [27]. In addition, there was a significant improvement in memory performance (cognitive Z score) in the fish oil *vs* placebo group ($p= 0.001$)[27]. In a second study investigating n-3 polyunsaturated fatty acid supplementation (480mg DHA + 720mg EPA daily for 6 months *vs* placebo)[28], borderline statistical significance ($p=0.047$) was reported between intervention and control for working memory. However, a third study investigating 625mg EPA+600mg DHA *vs* placebo showed no significant improvements in memory[29]. A fourth study who investigated DHA supplementation only (2mg/day *vs* placebo)[30], found significant improvements for short-term memory ($p = <0.0001$) and long-term memory ($p = <0.0001$) in comparison to the placebo group. In a trial investigating the effect of cocoa flavanols (High Flavonols (HF) 990 mg *vs* Intermediate Flavonols (IF) 520 mg *vs* Low Flavonols (LF) 45 mg of flavanols daily for 8 weeks)[34], verbal fluency test scores significantly improved ($p = 0.0001$), with a significantly greater score in HF participants in comparison with the LF group ($p = <0.05$).

B vitamin supplementation[25] (0.8mg folic acid, 0.5mg vitamin B12, 20mg vitamin B6 daily for 2 years), demonstrated improvement in verbal memory but only in those participants with low baseline B vitamin/folic acid status. The odds of correctly remembering a word in the HVLT test were 69% greater for a person in the high tHcy group if they were taking B vitamins, than if they were taking placebo (OR =1.69, $p=0.001$)[25]. For category fluency (CERAD), in the high tHcy group, the average number of words was 9.4% greater at follow up in those on B vitamin treatment compared with the placebo ($p= 0.04$). However, in the low tHcy group (indicating higher B vitamin/folic acid status) there was no significant difference between the treatment group and placebo[25]. In another B vitamin study, investigating folic acid alone (400 µg daily for 6 months) *vs* conventional treatment[24] results showed for short term memory that the intervention group had a significant increase in score from baseline to 6 months in comparison to the control ($p = <0.001$). Results also indicated that elevated homocysteine levels at baseline were associated with significantly poorer cognitive performance at intervention completion for the intervention group in comparison to the control[24].

Vitamin E supplementation (2000IU daily for 2 years)[31], the medical food, Souvenaid containing the specific nutrition combination Fortasyn Connect (125ml daily)[33] and Chromium picolinate (CrPic) supplementation (1000 mcg daily for 12 weeks)[32] had no significant improvement in comparison to placebo for memory. Supplementation with CrPic showed significantly reduced intrusion errors, with the intervention group making significantly fewer errors on CVLT for learning (p = 0.01) than the placebo group, however there was no significant reduction for recall and recognition memory[32]. In an investigation of the effects of a high carbohydrate diet (50% of total calories) *vs* a very low carbohydrate (5-10% of total calories) diet in participants with MCI[12], pre-intervention carbohydrate levels were recorded as 207g for those in the "high" carbohydrate group and 190g in the "low" carbohydrate group. Post-intervention carbohydrate levels measured 197g for the "high" carbohydrate group and 34g for the "low" carbohydrate group. These figures indicate that those in the "low" group had a major dietary change whereas the "high" group could be regarded as a control. Results showed no significant effect of the intervention for memory performance (brief visuospatial memory test, story recall and word list) between intervention and control groups[12]. Concord grape juice[35] (daily consumption between 6-9ml/kg for 12 weeks) significantly improved verbal learning compared to the placebo (p = 0.04). However, there were no significant differences between those consuming the grape juice and placebo for delayed verbal recall and spatial memory[35]. Furthermore, wild blueberry juice[36] (daily consumption between 6-9 mL/kg for 12 weeks) had a significant improvement from baseline score to 12 weeks for V-PAL cumulative learning (p= 0.009). In addition, mean scores for CVLT word list recall improved significantly within the intervention group from baseline to 12 weeks (p = 0.04). There was a significant difference in V-PAL score between intervention and control groups (p = 0.03), however no significant difference was observed for CVLT performance between groups[36].

Executive Function

The domain of executive function was measured by 12 tests (table 3). For this cognitive domain, measured within nine studies (56%), two RCTs showed a statistically significant improvement between groups at study completion[25,34]. At 24 months follow-up, the odds of a correctly drawn item from CLOX1, after controlling for confounders (CLOX2 at follow-up, CLOX1 at baseline, age, education, APOE Ɛ4 status and sex), was 30% greater in those receiving B-vitamins *vs* placebo (p = 0.02)[25]. For cocoa flavonol supplementation[34], better scores for trail making test, part B (p = <0.05) were reported among participants who received HF and IF treatments *vs* the LF group. In addition, the time required to complete the trail making task, B significantly changed during the duration of the study (p = <0.0001). However, DHA+EPA supplementation[27,29], nutritional counselling with calorie restriction[37], high fat/high GI *vs* low fat/low GI diet[38], high carbohydrate *vs* low

carbohydrate diet[12], supplementation with Fortasyn Connect (Souvenaid)[33] and vitamin E[31] showed no significant difference in cognitive function tests between groups at study completion. There was a significant improvement in comparison with placebo at six months for those consuming vitamin E supplements ($p<0.05$)[31]. However, thereafter, this significant difference was not maintained beyond this time point.

Attention

As shown in table 3, five of the 16 (31%) included studies measured the domain of attention. Nutritional counselling *vs* standard care showed no significant change in attention between groups after 12 months[37]. Whereas, cocoa flavonol supplementation[34], significantly better scores for trail making test, part A ($p = <0.05$) were reported among participants who received HF and IF treatments in comparison to the LF group. In addition, the time required to complete the trail making task, part A significantly changed during the duration of the study ($p=<0.0001$)[34]. DHA+EPA supplementation[27] (one study) showed a significant improvement in digit span score from baseline to 12 months in the fish oil group *vs* placebo ($p = <0.0001$)[27]. However, there was no significant treatment effect reported between the fish oil and placebo groups for any of the other measures of attention[27]. Supplementation with DHA only[30] showed significant improvements in digit span score in comparison to the placebo ($p=<0.0001$). However, a third study with DHA+EPA supplementation[29] found no significant differences between groups for attention.

Language

Two of the 16 (13%) studies measured the cognitive domain of language (table 3). There were no significant differences between groups for nutritional counselling with calorie restriction[37]. For vitamin E supplementation[31], there was a significant difference in score from the baseline value between groups at 6 months ($p = <0.05$), 12 months ($p = <0.05$) and 18 months ($p = <0.05$), however, thereafter this significant difference was not maintained until intervention completion (36 months)[31].

Visuospatial skills

Four studies (25%) measured the cognitive domain of visuospatial skills (table 3). Supplementation with folic acid was the only study to show a significant interaction effect between groups for visuospatial skills ($p =0.03$)[24]. In addition, higher baseline homocysteine levels were associated with poorer cognitive performance on the block design test at the end of the intervention in comparison with the placebo (estimate value = −0.079, $p = <0.001$)[24]. Fish oil supplementation with concentrated DHA+EPA[27] , DHA[30] or vitamin E supplementation[31] did not show any significant differences between groups.

Global Cognitive Function

For cocoa flavonol supplementation[34] (supplementary material table 2), there was no significant change in MMSE score between the HF, IF or LF treatment groups over the duration of the study (p = 0.13). However, results also showed that the composite cognitive Z score significantly changed during the study (p=<0.0001). The cognitive Z score at the end of the study follow-up was significantly (p=<0.05) better in the HF group in comparison to the LF group[34]. Vitamin B supplementation[25] indicated no significant effect of treatment (p=0.57) on global cognition as measured by MMSE. However, analysis did show that those who had high baseline concentrations of homocysteine and were treated with B vitamins, were 1.58 more likely to provide a correct answer on the MMSE test than the placebo group (p <0.001). However, there was no significant difference for those with low baseline homocysteine, between the B vitamin or placebo groups. Similarly, fish oil supplementation[27] (one study) showed no statistically significant differences between groups for cognitive function as measured by the MMSE. Furthermore, vitamin E supplementation[31] at 6 months intervention showed a significant difference in comparison with placebo for overall cognitive function calculated by a composite Z score (p=<0.01). However, at 36 months this significant difference between groups was not maintained.

Assessment of Methodological Quality and Risk of Bias

The quality[22] of the 16 included studies varied, with eight studies achieving the maximum total score of 5[25-28,30,31,33,34] (supplementary material table 3). Thus, it was deemed that these studies stated appropriate randomisation processes, were clearly indicated as double blinded and the authors accounted for any participant withdrawals during the study. Two studies[12,38] scored one on the Jadad scale[22] and stated that participants were randomised however did not specify the randomisation process, if double-blinding took place and if any participant withdrawals occurred. Low risk of bias scores[23] were allocated for selection bias (n=9)[24-28,30,31,33,34], performance bias (n=7)[25,26,28,29,30,33,34], attrition (n=9)[24,25,27-30,33,34,37] and detection bias (n=6)[24,26,30,33,34,37] (supplementary material table 4). A high risk score was documented for detection bias (n=3)[12,38] and performance bias (n=2)[12] as there were no details provided of any double blinding method used.

Discussion

The aim of this systematic review was to examine the effect of diet, either alone or in combination with lifestyle and/or cognitive strategies, on cognitive health outcomes in patients with MCI. Together with the limited number of RCTs conducted and the heterogeneity of the studies in this review, a narrative synthesis of the findings was implemented. Studies varied greatly in terms of the nature of dietary intervention and cognitive outcome measures used. Furthermore, there were no studies that

measured the effectiveness of lifestyle and/or cognitive strategies in combination with their dietary intervention. Overall, it was evident that the findings were inconsistent across the studies and do not provide clear evidence to support the effect of any specific diet or dietary component on cognition in MCI patients.

Diet has been suggested to have a significant association with cognitive decline and progression to dementia, particularly showing a protective role against the harmful effects of neuro-inflammation and oxidative stress[40]. Although the pathways related to their role are complex and variable throughout the literature[14,15,16,41] it is thought that antioxidants in foods such as fruit and vegetables help to reduce oxidative stress levels in the brain and n-3 PUFAs in foods such as oily fish, are additionally linked to reduced inflammation[8]. There are plausible suggestions to support these mechanisms by the results of this review. There were some improvements in cognitive function, particularly in the domain of memory, reported for polyphenol compounds (e.g. cocoa flavonols[34]), fish oil supplementation with concentrated DHA+EPA[27,28] or DHA alone[30] and beverages which are high in these bioactive, antioxidant properties e.g. Cocord grape juice[35] and wild blueberry juice[36]. However, some of these studies either had small, potentially underpowered sample sizes, used a limited number of cognitive tests to measure outcomes or had shorter intervention durations therefore these results should be interpreted with caution.

Nutrient and Food Supplementation

As mentioned, antioxidant compounds such as vitamins A, C and E have a role in regulation of oxidative stress, a pathway linked with neurodegeneration and cognitive decline[42]. However in this review, diet supplementation with vitamin E[31] had no significant effect on progression from MCI to dementia and/or AD or on cognitive function at intervention completion. Furthermore, meta-analyses have reported no significant effect of vitamin E on cognitive function outcomes[43,44]. The particular form of vitamin E used could have an influence on the impact of this nutritional component on cognitive decline, with research suggesting total tocopherol plasma concentrations rather than single tocopherols may be more valuable at predicting cognitive impairment, particularly AD[45]. Furthermore, as we consume foods in complex patterns, resulting in ingestion of combinations of various forms of vitamin E, it may be more beneficial to focus research efforts away from single forms and follow a more holistic investigation[15]. In this review, supplementation with cocoa flavonols[34] showed better cognitive performances for those who received higher flavonols concentrations compared to lower concentrations. There are suggestions in the literature that flavonoids may exert their neuroprotective properties in a similar mechanism to antioxidants in the body[46]. However, further indications suggest that flavonoids may have a more prominent role in the

384 regulation of neuronal signalling pathways[47] or neuro-inflammation[48]. It is clear that further
385 research is required to fully explore the mechanism of action of flavonoid compounds and investigate
386 the potential role they may have in protecting against cognitive decline[49].
387
388 Low folate and B vitamin status is linked to cognitive dysfunction during the ageing process and
389 better cognitive performances have been associated with higher intakes of B vitamins[50,51,52].
390 Furthermore, increased levels of homocysteine have been linked to poorer cognition, particularly in
391 memory and attention[53,54,55]. This may be explained by the role that B vitamins have in one-carbon
392 metabolic pathways in the body, acting as co-factors for the remethylation of homocysteine to
393 methionine, producing the methyl-donor, S-adenosylmethionine. This methyl donor has a specific
394 role in the methylation of phospholipids and neurotransmitters in the brain, thus indicating how a
395 depletion in B vitamins status may influence cognitive function and ultimately, cognitive
396 impairment[56,57]. In this review, supplementation with a B vitamin combination[25] or with folic acid
397 alone[24] had significant effects on executive function[25] and furthermore, when baseline
398 homocysteine levels were elevated, there were significant improvements in global cognition[25],
399 memory[24,25] and visuospatial skills[24]. In support, not only have improvements been observed in
400 performance based cognitive tests, B vitamin supplementation (folic acid, vitamin B6 and B12
401 combination) have resulted in reduced rates of brain atrophy in MCI[58,59]; a process which could
402 result in progression to AD if allowed to advance. However, findings are mixed with meta-analyses
403 of clinical trial data reporting no significant effect of B vitamins on cognitive function[43,60].
404 Therefore, further trial research is warranted to confirm the role of B vitamins in reducing cognitive
405 decline.
406
407 Polyunsaturated fatty acids have been associated with promoting cognitive function, primarily as a
408 result of their anti-inflammatory properties[61]. Furthermore, n-3 fatty acids, particularly DHA, are a
409 key component of neuronal membranes in the brain, influencing neurogenesis and neuronal
410 function[41,62]. In this review, supplementation with DHA+EPA[27,28] reported significant
411 improvements in the domain of memory, with DHA supplementation alone[30] showing an additional
412 improvement in attention, albeit by a single cognitive test. In contrast, evidence from meta-analyses
413 have reported no significant effect of omega 3 fatty acids on cognitive outcomes[43,62]. Furthermore,
414 it has been suggested that fatty acid supplementation in individuals who are homozygous carriers of
415 the APOE Ɛ4 allele, a risk factor for cognitive decline, could be resistant from the potential protective
416 effects of fatty acids on cognitive health[63]. Thus, this is an important covariate to consider when
417 designing trials to test effectiveness of fatty acid supplementation. However, some observational
418 evidence does exist to support the role of n-3 fatty acids in promoting cognition with a study that

followed non-demented participants for 4 years, finding higher plasma EPA concentrations to be associated with a lower incidence of dementia[64]. In addition, an intervention study with older adults with subjective memory impairment investigated fatty acid supplementation (EPA+DHA) vs corn oil placebo[65]. Results showed significantly improved cortical blood oxygen level-dependent (BOLD) activity during a working memory task in the fish oil group compared to placebo. In this review, one study investigating DHA+EPA supplementation[29] found no effect on cognitive function in comparison to control. A plausible explanation for this finding could be that the placebo used this study was olive oil, a component of the Mediterranean Diet associated with improved cognitive function owing to its anti-inflammatory properties[66]. Therefore, further investigation of the role of fatty acids and cognitive decline is justified through well-designed, robust studies.

Whole-foods/dietary patterns

Only three of the 16 studies included in this review[12,37,38], focused their diet intervention on "whole-foods/dietary patterns" rather than single-nutrient supplements or single food products. In everyday situations, individuals consume holistic dietary patterns which involve complex interactions between nutrients[67]. It therefore could be suggested that the more representative intervention design to measure the effects of diet on cognition could be that which involved a dietary pattern rather than focused on a single nutrient. In this review however, these studies were heterogeneous in terms of the dietary intervention and reported mixed findings. Research evidence suggests that ketogenic diets[68] and calorie restriction[69] may have a promising, yet under-investigated, role in AD prevention, suggesting links to brain glucose metabolism[68], reduction in oxidative stress[69], and anti-inflammatory mechanisms[69]. There is also emerging evidence from observational studies to suggest a protective role for healthy dietary patterns such as the Mediterranean Diet (MD) on MRI measured brain structures[70,71,72] and therefore further investigation of such dietary patterns is necessary, with the inclusion of more rigorous assessment measures, to help to provide insight into potential mechanisms of how diet can impact brain health.

Use of Biomarkers and Cognitive Markers

CSF biomarkers may be a valuable asset in detecting pathological changes in neurological diseases, owing to the processes of extracellular amyloid-β deposition and accumulation of hyperphosphorylated tau proteins[73]. One study[38] in this review included biomarker analysis in addition to cognitive test measures. Increased concentrations of CSF Aβ42 were observed in those with aMCI consuming a low diet (low saturated fat/low GI) in comparison to healthy controls who observed a decrease in CSF Aβ42 levels (supplementary material). Thus, CSF biomarkers in this study changed in response to diet in aMCI patients in the absence of any discernible changes in

cognitive function test scores, albeit in very small sample. These differences could provide insights into the mechanisms of action of beta-amyloid in the body in cognitive impairment. In particular, biomarker analysis may be more sensitive to dietary changes and could be an important consideration for future dietary intervention studies as the use of biomarkers could be a more rigorous approach to assess cognitive performance in this patient group[74]. Furthermore, it has been suggested that the use of brain imaging as a cognitive marker such as MRI scanning is a more robust measure of cognition in comparison to questionnaire based tests[50,75]. Three studies in this review reported on cognitive marker information, including MRI[30,33] and fMRI imaging[32], as an additional outcome measure for cognitive function, depicting some significant interaction effects for the intervention group that were not entirely reflected by cognitive function tests (supplementary material). Brain imaging techniques have been used in nutrition and cognition research, with investigations into B vitamins utilising MRI scanning to detect changes in brain atrophy in MCI[58,59], fMRI scanning to explore fish oil supplementation in older adults with subjective memory impairment[65] as well as investigations of beta-amyloid load using positron emission tomography (PET) and neuronal activity via PET imaging with 2-[^{18}F]fluoro-2-Deoxy-D-glucose (FDG)[76]. Therefore, the use of these higher quality methods could be implemented in future dietary intervention trials to comprehensively measure the potential effects of diet on cognition and explore mechanisms.

The mixed evidence found on the effect of diet on cognition among MCI participants may be explained by the heterogeneity of studies included, owing to variation in cognitive outcome measures used, differences in the diet intervention type (supplements *vs* single food products *vs* dietary patterns), variations in sample size and duration of intervention. Furthermore, the small number of dietary intervention studies conducted among this patient group make it difficult to provide conclusive evidence to support the effect of diet on cognitive outcomes. Of the 16 included studies, those with B vitamin and/or folic acid supplementation[24,25], DHA/EPA supplementation[27,28,30] or cocoa flavonol rich drinks[34] appeared to have the most consistent effects on cognitive outcomes. However, it is difficult to confirm that these dietary interventions are the most effective in terms of promoting cognitive function due to the low number of studies testing the same intervention. Nonetheless, the outcomes of the systematic review highlight the need for well-designed, robust RCTs, with pretested and informed methodological characteristics to further explore the role of diet in cognitive decline.

Limitations

During the literature search for this review, a broad search strategy was used to ensure the search covered all related aspects to the reviews aims and objectives. However, search limitations were set

to only include studies in English language and the grey literature was not included for this review, therefore this could have resulted in language and publication bias. As RCTs were the study design of choice for inclusion, this may have caused selection bias. However, as RCTs are considered the best design for assessing the effect of a dietary intervention with their ability to identify causality[77], this therefore provides justification for the decision. Pilot studies were not included in this review, as these studies are likely to have an underpowered sample size. The number of studies included in this review were small, however, as there are few RCTs completed in this area, this supports the need for further intervention studies to increase the evidence-base. Due to the heterogeneity of the included studies, the data was not meta-analysed. Instead, a rigorous narrative review was implemented. Study characteristics, such as short study durations, may have not provided sufficient time to view a change in cognitive outcomes. It has been suggested that long term, RCTs are the best approach in the design of a nutritional intervention to measure cognitive performance, with estimations that the most effect preventative trials require up to 3-5 years duration and follow-up[78]. Furthermore, ensuring a sufficient sample size though determination by a power calculation will provide a more stringent approach to the research design. Therefore, it is important when designing intervention studies that duration and sample size are pre-tested, though a feasibility study or by comparison to similar studies in the field.

Eight of the 16 studies in this review achieved the maximum quality score as assessed by the Jadad scale[22]. Those studies who received the lowest scores failed to provide details on the randomisation and blinding processes which took place in the study. It is important to note however, as both studies involved a dietary pattern intervention rather than a supplement/placebo, it is impractical to ensure participants and researchers are blinded to the intervention group. Therefore, the decision that these studies are of "low quality" is difficult to confirm. Furthermore, for risk of bias, a number of studies were allocated uncertain risk for selection, performance, attrition and detection bias due to inadequate information on randomisation, double blinding and/or withdrawals. Finally, a challenge within this review was the heterogeneity of cognitive outcome measures used to determine cognitive change. Some studies grouped results by domain, while others by the single cognitive tests used. This made it difficult when presenting the results of this review, as some study results did not exactly fit within the cognitive domains, as these were not specified in the original paper. In line with the NIA-AA criteria for the diagnosis of MCI[3], which state that for a diagnosis of MCI individuals must have deterioration in one or more cognitive domains, it would be beneficial for analysis purposes if future intervention studies could assess cognition based on these domains to allow better comparison of results. However, in saying that, even the tests used to measure cognition within domains vary greatly and there is a lack of standardisation. It is evident therefore, that there is a demand to determine a

specialised cognitive test battery that can be used to measure change in cognition, particularly within an MCI population. Furthermore, change in cognition requires time, more rigorous examinations and evaluation by clinical specialist[79]. These are all important considerations for future intervention trials going forward.

Conclusion

To date there is insufficient RCT evidence on the effect of whole diets or specific dietary components on cognitive outcomes in MCI patients. Existing studies are heterogeneous in terms of the dietary intervention, duration, sample size and cognitive outcome measures assessed, with the most consistent results for cognitive function shown by B vitamins, folic acid, DHA and/or EPA and cocoa flavonol supplementation. Further exploration of the potential beneficial effect of diet on cognitive outcomes in MCI is merited.

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Table 1: An overview of the inclusion and exclusion criteria for this systematic review

	Inclusion Criteria	Exclusion Criteria
Study design	Randomised controlled trial (RCT)	Observational study design; Pilot studies, when a paper clearly stated that the research was a "pilot study"
Intervention	Dietary Intervention either diet alone (a dietary pattern or dietary supplements) or in combination with lifestyle and/or cognitive strategies	Medical type intervention in conjunction with either a diet/lifestyle/cognitive intervention with undifferentiated results
Control	Control interventions that were not expected to have specific risk-modifying effects; Control arms would typically involve no intervention, usual diet or placebo.	Studies with no comparator, placebo or control
Diagnosis of MCI	Diagnosis of MCI was necessary by a medical physician or according to internationally accepted and validated classifications or criteria	"Memory problems" or "self-reported memory complaints" and no clear diagnosis of MCI; A diagnosis of dementia or any other form of cognitive impairment other than MCI, unless results for MCI participants were presented separately; "Cognitively healthy adults"
Participants	Community dwelling participants; No restrictions made based on gender or age	Individuals who were hospitalised, in a rehabilitation or long-term care facility; Participants with psychiatric problems e.g. depression or any significant medical comorbidity, or history of, a comorbid condition that may alter performance on cognitive tests, e.g. stroke, head injury, Parkinson's disease, learning disability

Table 2: Overview of study characteristics

Author, Year and Location	MCI sample characteristics	Diagnostic Criteria for MCI	Intervention	Study Duration	Outcome Measures
Bayer-Carter et al., 2011[38] (n=49) USA	68.4 years aMCI = 29 High = 15 Low = 14 Healthy Controls = 20 High = 9 Low = 11 Lost to follow up = *no detail*	Petersen (2004)[82]	***Intervention groups:*** (1) High diet- 45% fat (saturated fat 25%), 35-40% carbohydrate (glycaemic index >70) and 15-20% protein. (2) Low diet- 25% fat (saturated fat <7%), 55-60% carbohydrate (GI <55) and 15-20% protein. ***Control group:*** Healthy adult control group.	4 weeks	**Immediate and delayed memory:** Story recall, word list, brief visuospatial memory test; **Executive Function**: Trail making test part B, Stroop test, Verbal fluency test; **Motor speed**: Trail making test part A, Stroop test; **AD biomarkers** CSF Aβ42, CSF Aβ40, tau protein phosphorylated tau (p-tau), Apolipoprotein E (APOE)
Horie et al., 2016 (n=80)[37] Brazil	68.1 years Intervention = 40 Control = 40 Lost to follow up = 5	European Consortium on Alzheimer's Disease [80]	***Intervention group:*** caloric restriction and counselling with nutritionists (26-28 x1 hour meetings). Advice- eating a diet rich in fibre, fruits, vegetables, wholegrains and included at least 1g/kg body weight of protein per day. Recommended calorie deficit of approx. 500 kcal/day (min 1200kcal per day). ***Control group:*** conventional medical care with consultant Geriatrician. All participants were advised to engage in physical activity (at least 150 minutes per week of moderate intensity aerobic activity or walking)[35]	12 months	**Verbal Memory**: RAVLT delayed recall, total learning and recall recognition**; Attention:** Digit span forward, Digit span backward, Trail making test part A**; Working Memory:** Digit span backwards, Trail making test part**; Psychomotor processing speed**: Trail making test part A, Trail making test part B**; Executive Function**: Modified Wisconsin Card Sorting Test, Trail making test part B, verbal fluency; **Language**: Phonemic verbal fluency, Semantic verbal fluency
Krikorian et al., 2012 [12] (n=23) USA	70.1 years High Carbohydrate = 11 Low Carbohydrate = 12 Lost to follow up =0	Clinical Dementia Rating (CDR) [81]	***Intervention groups:*** High carbohydrate (50% of total calories) *vs* a very low carbohydrate group (5-10% total calories). Intake of protein and fat were allowed to vary and total calorie intake was not restricted	6 weeks	**Working memory and executive ability:** Trail making test, part B **Secondary or long term memory:** Verbal paired associate learning test (V-PAL)

Table 2: Overview of study characteristics

Author, Year and Location	MCI sample characteristics	Diagnostic Criteria for MCI	Intervention	Study Duration	Outcome Measures
de Jager et al., 2012[25] (n= 266) UK	76.8 years Intervention = 133 Control = 133 Lost to follow up = 43	Petersen Criteria (2004)[82]	***Intervention group:*** 0.8mg folic acid, 0.5mg vitamin B12, 20mg vitamin B6 (daily). ***Control group:*** vitamin-free tablets of similar appearance.	2 years	**Global cognition**: MMSE; **Episodic Memory**: HVLT-R; **Semantic Memory**: Category fluency CERAD; **Executive Function**: CLOX; **Clinical outcome measures**: CDR
Ma et al., 2016[24] (n=180) China	65 years Intervention = 90 Control = 90 Lost to follow up = 21	Petersen Criteria (2004)[82]	***Intervention group:*** oral folic acid (400 µg/day). Participants were instructed to supplement with one tablet daily, during, or immediately after a meal. ***Control group:*** Conventional medical treatment	6 Months	**Chinese version of the WAIS-RC-** Information, Similarities, Vocabulary, Comprehension, Arithmetic, Digit Span, Block Design, Picture Completion, Digit Symbol-Coding, Object Assembly & Picture Arrangement
DeKosky et al., 2008[26] (total study n= 3069, n=482 with MCI) USA	79.1 years Intervention = 256 Control = 226 Lost to follow up: 195 (total study)	International Working Group on MCI Guidelines[83]	***Intervention group:*** twice-daily doses of 120-mg G biloba extractor. ***Control group:*** received an identically appearing placebo	6.1 years	Diagnosis of Dementia by DSM-IV Criteria, Modified MMSE, CDR, ADAS-Cog
Lee et al., 2013 (n=36)[27] Malaysia	65.0 years Intervention = 18 Control = 18 Lost to follow up = 1	Petersen Criteria (2004)[82]	***Intervention group***: 3 x 1-g soft gelatine capsules each day, each containing 430 mg of DHA and 150 mg of EPA. ***Control group:*** isocaloric placebo corn oil (0.6 g linoleic acid)	12 months	**Memory:** Visual reproduction I and II, Rey Auditory Verbal Learning Test (RAVLT), Digit span backward; **Executive Function and attention**: Clock drawing test (CDT), Digit span forward; **Psychomotor speed:** Digit symbol substitution test; **Visuospatial skills:** Matrix reasoning, Block design**; Global cognitive function**: MMSE

Table 2: Overview of study characteristics

Author, Year and Location	MCI sample characteristics	Diagnostic Criteria for MCI	Intervention	Study Duration	Outcome Measures
Petersen et al., 2005[31] (total study n=769) USA and Canada	72.9 years Donepezil = 253 Vitamin E = 257 Placebo = 259 Lost to follow up: 230 (total study)	Petersen (1999)[84]	***Intervention group***: (1) 2000 IU of vitamin E, placebo donepezil, and a multivitamin daily; (2) 10 mg of donepezil, placebo vitamin E, and a multivitamin daily. The multivitamin contained 15 IU of vitamin E. The initial dose of vitamin E was 1000 IU daily, and the dose was increased to 2000 IU (1000 IU twice daily) after six weeks. ***Control group:*** received a placebo vitamin E, placebo donepezil, and a multivitamin daily.	3 years	**Primary end-point:** time to development of possible of probable Alzheimer's disease**; Secondary:** MMSE, ADAS-Cog, Global CDR CDR sum of boxes, The Global Deterioration Scale Neuropsychological Battery consisting of: New York University paragraph recall test, Symbol Digit Modalities test, category fluency test, number-cancellation test, Boston naming test, digits-backwards test, clock drawing test, Maze tracing task
Desideri et al., 2012[34] (n=90) Italy	71.2 years High = 30 Medium = 30 Low = 30 Lost to follow up: 3 (included in analysis)	Petersen Criteria (2004)[82]	***Intervention group:*** once daily a dairy-based cocoa drink containing cocoa flavanols either at - (1) high (HF; _990 mg of flavanols per serving) (2) intermediate (IF; _520 mg of flavanols per serving) (3) low level (LF; _45 mg of flavanols per serving)	8 weeks	MMSE, Trail Making Test A and B, Verbal Fluency Test
Krikorian et al., 2010a[35] (n=12) USA	72.8 years Male and female Intervention = 5 Control = 7 Lost to follow up = 0	Clinical Dementia Rating (CDR)[81]	***Intervention group:*** 100% Concord grape juice. A dosing schedule was instituted determined by body weight to maintain daily consumption between 6-9ml/kg, a range consistent with other human grape juice trials. Taken daily in equal, divided dosages with the morning, midday and evening meals ***Control:*** contained no juice or natural polyphenol	12 weeks	**Memory**: California Verbal Learning Test (CVLT), Spatial Paired Associate Learning Test

Table 2: Overview of study characteristics

Author, Year and Location	MCI sample characteristics	Diagnostic Criteria for MCI	Intervention	Study Duration	Outcome Measures
Krikorian et al., 2010b[36] (n=9) USA	76.2 years Male and female Intervention = *No detail* Control = *No detail* Lost to follow up= *No detail*	Clinical Dementia Rating (CDR)[81]	***Intervention group:*** Wild Blueberry Juice prepared from ripe, frozen wild (lowbush) blueberries. Taken daily in equal divided dosages with morning, mid-day and evening meals. Daily consumption was maintained between 6- 9 mL/kg by using a dosing schedule determined by body weight. ***Control:*** contained no juice or natural polyphenol	12 weeks	**Memory**: Verbal Paired Associate Learning test (V-PAL), California Verbal Learning Test (CVLT)
Krikorian et al., 2010c[32] (n=26) USA	71.0 years Intervention = 15 Control = 11 Lost to follow up = *no detail*	Clinical Dementia Rating (CDR)[81]	***Intervention group:*** chromium picolinate (CrPic) containing 1000 mcg elemental chromium. ***Control group:*** placebo – no details	12 weeks	**Memory**: California Verbal Learning Test (CVLT) fMRI scanning
Bo et al., 2017 (n=86)[28] China	71.1 years Intervention = 42 Control = 44 Lost to follow up = 22	Petersen Criteria (1999)[84]	***Intervention group:*** 625mg DHA + 600mg EPA (twice daily) ***Control group:*** placebo capsules containing olive oil (twice daily)	6 months	Basic Cognitive Aptitude test (BCATs): digit copy, Chinese character comparison, mental arithmetic, Chinese character rotation, recall answer of mental arithmetic, recognition of two-word nouns, and recognition of meaningless figures. These seven sub-items were divided into five sections: perceptual speed (PS), mental arithmetic efficiency (MAE), space imagery efficiency (SIE), working memory (WM), and recognition memory (RM)

Table 2: Overview of study characteristics

Author, Year and Location	MCI sample characteristics	Diagnostic Criteria for MCI	Intervention	Study Duration	Outcome Measures
Soininen et al., 2017[33] (n=311) Finland	71.0 years Intervention = 153 Control = 158 Lost to follow up/ discontinued = 66	Dubois et al., (2007)[85]	***Intervention group:*** Medical food Souvenaid, a 125 ml once-a-day drink containing the specific nutrient combination Fortasyn Connect (1200mg DHA, 300mg EPA, 106mg Phospholipids, 400mg Choline, 625mg UMP, 40mg Vitamin E, 80mg Vitamin C, 60 mcg selenium, 3 mcg vitamin B12, 1mg vitamin B6, 400 mcg Folic acid) ***Control group:*** 125 ml once-a-day control drink	24 months	**Primary end points:** Composite Z score based on Consortium to Establish a Registry for Alzheimer's disease (CERAD) 10-word list learning immediate recall, CERAD 10-word delayed recall, CERAD 10-word recognition, category fluency, and letter digit substitution test (LDST). **Memory** (CERAD 10-word list learning immediate recall, delayed recall, and recognition); **Executive function** (category fluency, Wechsler Memory Scale revised digit span total score, concept shifting test condition C [corrected for the zero trials], and LDST); neuropsychological test battery (NTB) total (composite Z score based on all 16 items of the NTB); **Secondary end points:** Clinical Dementia Rating- Sum of boxes (CDR-SB); Brain volumes based on MRI; Progression to dementia by DSM-IV Criteria
Zhang et al., 2017 (n=240)[30] China	74.5 years Intervention = 120 Control = 120 Lost to follow up = 21	Petersen Criteria (2004)[82]	***Intervention group:*** DHA supplementation (2g/day) ***Control group:*** corn oil	12 months	Chinese version of the Wechsler Adult Intelligence Scale Revised (WAIS-RC). The WAIS-RC includes 11 sub-tests: Information, Similarities, Vocabulary, Comprehension, Arithmetic, Digit Span, Block Design, Picture Completion, Digit Symbol-Coding, Object Assembly, and Picture Arrangement

Table 2: Overview of study characteristics

Author, Year and Location	MCI sample characteristics	Diagnostic Criteria for MCI	Intervention	Study Duration	Outcome Measures
Phillips et al., 2015[29] (n=57) UK	68.7 years Intervention = 29 Control = 28 Lost to follow up = 2	Petersen Criteria (2004)[82]	***Intervention group:*** 625mg DHA + 600mg EPA (twice daily) ***Control group:*** placebo capsules containing olive oil (twice daily)	4 months	MMSE; Hopkins Learning Test Revised and neuropsychological measures of executive functioning, language, verbal reasoning, visual memory

Table 3: Summary table of cognitive function results grouped as per NIA-AA (Albert et al., 2011) criteria

NIA-AA Cognitive Domain	Study	Intervention	Cognitive Function Measure used	Intervention group and Control Group Results	Between Group Difference
Memory	Horie et al., 2016[37]	Nutrition counselling & calorie restriction *vs* standard care	RAVLT (delayed recall)	Intervention (mean change 0.7, 95% CI -0.9±2.3); Control (mean change 1.7, 95% CI 0.1±3.3)	-
			RAVLT (total learning)	Intervention (mean change 3.3, 95% CI -1.3±7.9); Control (mean change 2.0, 95% CI -2.6 ±6.7)	-
			Digit span backward	Intervention (0.2, 95% CI -0.8±1.2); Control (0.1, 95% CI -0.9±1.1)	-
			Trail making test, part B	Intervention (mean change -8.6, 95% CI -71.6±54.5); Control (mean change 5.1, 95% CI -58.3±68.6)	-
	Lee et al., 2013[27]	Fish oil supplementation with concentrated DHA+EPA *vs* placebo	RAVLT (delayed recall)	Intervention (baseline mean score 6.7, 95% CI 4.897–8.442 – 12 months mean score 8.1, 95% CI 6.645–9.462); Control (baseline mean score 6.1, 95% CI 4.431–7.860- 12 months mean score 5.0, 95% CI 3.587–6.312)	✓
			Visual reproduction I	Intervention (baseline mean score 20.0, 95% CI 15.234–24.820 – 12 months mean score 29.2, 95% CI 25.207–33.269); Control (baseline mean score 21.0, 95% CI 16.394–25.666 – 12 months mean score 23.1, 95% CI 19.154–26.952)	✓
			Visual reproduction II	Intervention (baseline mean score 13.3, 95% CI 8.297–18.362 – 12 months mean score 20.8, 95% CI 15.564–26.110); Control (baseline mean score 12.6, 95% CI 7.710–17.445 – 12 months mean score 18.0, 95% CI 12.943–23.143)	-
			Digit symbol substitution	Intervention (baseline mean score 5.5, 95% CI 3.723–7.218 – 12 months mean score 5.5, 95% CI 3.723–7.218); Control (baseline mean score 4.9, 95% CI 3.254–6.634 – 12 months 4.9, 95% CI 3.254–6.634)	-
			Memory Cognitive Z-score	Intervention (mean change 0.96 (SD 0.76)**); Control (mean change 0.16, (SD 0.59))	✓
	Petersen et al., 2005[31]	2000 IU vit E, 10mg donepezil, or placebo	Memory Z Score (ADAS recall scores & New York University recall scores)	Intervention (6 months, Z score -0.10, SD ±0.48; 36 months Z score -0.31, SD±0.59); Control (6 months, Z score -0.17, SD ±0.47; 36 months Z score -0.28, SD ±0.62)	-
	Ma et al., 2016[24]	oral folic acid (400 µg/day) *vs* conventional treatment	Digit Span	Intervention (baseline mean score 9.27 (SD ±3.11) - 6 months mean score 13.05 (SD ±3.07); Control (baseline mean score 8.87 (SD ±2.70) - 6 months mean score 9.75 (SD±3.14)	✓

RAVLT, Rey Auditory Verbal Learning Test; SD, Standard Deviation; HVLT-R, Hopkins Verbal Learning Test – Revised; tHcy, Total Homocysteine; GI, Glycaemic Index; aMCI, amnesic Mild Cognitive Impairment; SEM, Standard Error of the Mean; VPAL, Verbal Paired Associates Learning; CVLT, California Verbal Learning Test; CrPic, Chromium Picolinate; CDT, Clock Drawing Test; NTB, Neuropsychological Test Battery; *Statistically significant difference p≤0.05 within group; **Statistically significant difference p≤0.001 within group; ✓Statistically significant difference (p≤0.05) between intervention & control groups at study completion; - No statistically significant difference between intervention & control at study completion; † Statistically significant difference between intervention & control at stated time-point

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NIA-AA Cognitive Domain	Study	Intervention	Cognitive Function Measure used	Intervention group and Control Group Results	Between Group Difference
	De Jager et al., 2012[25]	0.8mg folic acid, 0.5mg vitamin B12 and 20mg vitamin B6 *vs* placebo	HVLT-R (subgroup analyses, with baseline tHcy levels)	The odds of correctly remembering a word from the list of 12 in the HVLT test were 69% greater for a person in the high tHcy group if they were taking B vitamins than if they were taking placebo (OR =1.69)	✓
			CERAD (subgroup analyses, with baseline tHcy levels)	The average number of words was 9.4% greater at follow up in those on B vitamin treatment in the high tHcy group, compared with the placebo (OR=0.09)	✓
	Bayer-Carter et al., 2011[38]	High fat/high GI diet *vs* Low fat/ low GI diet	Brief Visuospatial Memory Test	aMCI Low diet baseline mean score 7.39 (SEM 0.71) – week 4 mean score 8.31 (SEM 0.62); aMCI high diet baseline mean score 8.27 (SEM 0.66) – week 4 mean score 8.40 (SEM 0.58); Healthy controls High diet baseline mean score 9.89 (SEM 0.85) – week 4 mean score 9.56 (SEM 0.74); Healthy controls low diet baseline mean score of 8.27 (SEM 0.77) – week 4 mean score 9.82 (SEM 0.67)	-
			Story recall	aMCI Low diet baseline mean score 18.48 (SEM 1.43) – week 4 mean score 21.46 (SEM 1.70); aMCI High diet baseline mean score 20.37 (SEM 1.31) – week 4 mean score 22.30 (SEM 1.59); Healthy controls High diet baseline mean score 22.69 (SEM 1.7 4)- week 4 mean score 23. 19 (SEM 2.04); Healthy controls Low diet baseline mean score 21.09 (SEM 1.55) – week 4 mean score 19.90 (SEM 1.95)	-
			Word list	aMCI Low diet baseline mean score 11.62 (SEM 0.76) – week 4 mean score 11.77 (SEM 0.80), aMCI High diet baseline mean score 11.33 (SEM 0.71); Healthy controls Low diet baseline mean score 13.27 (SEM 0.93) – week 4 mean score 13.27 (SEM 0.96), healthy controls High diet baseline mean score 12.79 (SEM 0.92) – week 4 mean score 13.67 (SEM 0.95)	-
	Krikorian et al., 2012[12]	High carbohydrate *vs* a very low carbohydrate	Trail making test, part B	Intervention (pre-intervention mean score 79.2 seconds *vs* post intervention mean score 82.9 seconds, F(1, 20) = 0.46, p = 0.50) Control (no detail)	-
			V-PAL	Intervention (pre-intervention mean score 11.8 seconds *vs* post intervention mean score 14.6 seconds, F(1, 20) = 6.45, p = 0.01); Control (no detail)	-

RAVLT, Rey Auditory Verbal Learning Test; SD, Standard Deviation; HVLT-R, Hopkins Verbal Learning Test – Revised; tHcy, Total Homocysteine; GI, Glycaemic Index; aMCI, amnesic Mild Cognitive Impairment; SEM, Standard Error of the Mean; VPAL, Verbal Paired Associates Learning; CVLT, California Verbal Learning Test; CrPic, Chromium Picolinate; CDT, Clock Drawing Test; NTB, Neuropsychological Test Battery; *Statistically significant difference p≤0.05 within group; **Statistically significant difference p≤0.001 within group; ✓Statistically significant difference (p≤0.05) between intervention & control groups at study completion; - No statistically significant difference between intervention & control at study completion; † Statistically significant difference between intervention & control at stated time-point

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NIA-AA Cognitive Domain	Study	Intervention	Cognitive Function Measure used	Intervention group and Control Group Results	Between Group Difference
	Krikorian et al., 2010a[35]	Concord grape juice supplementation *vs* placebo	CVLT learning	Intervention mean change 3.4; Control mean change 0.0; ANCOVA analysis intervention *vs* control F(1,8) = 5.55, p = 0.04, Cohen's f = 0.28	✓
			CVLT recall	Intervention mean change 1.2; Control mean change -0.4; ANCOVA analysis intervention *vs* control p = 0·10; Cohen's f = 0·35	-
			Spatial Paired Associate Learning Task	Intervention mean change 1.7; Control mean change -0.4; ANCOVA analysis intervention *vs* control p = 0·12; Cohen's f = 0·67	-
	Krikorian et al., 2010b[36]	Wild Blueberry juice supplementation *vs* placebo	V-PAL	Intervention (baseline mean score 9.3 *vs* week 12 mean score 13.2*); Control (no detail); ANCOVA analysis intervention vs control F(1,13) = 5.58	✓
			CVLT	Intervention (baseline mean score 7.2 *vs* week 12 mean score 9.6*); Control (no detail); ANCOVA analysis intervention vs control F(1,13), = 2.27	-
	Krikorian et al., 2010c[32]	Chromium picolinate (CrPic) supplementation *vs* placebo	CVLT Learning	Intervention *vs* Control mean score at 12 weeks (46.8 *vs* 45.8)	-
				Intrusion errors intervention *vs* control at 12 weeks (0.20 *vs* 1.27); F (1, 23) = 6.48; Cohen's f = 0.51)	✓
			CVLT Delay Recall	Intervention *vs* Control mean score at 12 weeks (9.4 *vs* 8.4)	-
				Intrusion errors intervention *vs* control at 12 weeks (0.98 *vs* 2.3), F (1, 23) = 3.35, Cohen's f = 0.35)	-
			CVLT Long Delay Recall	Intervention *vs* Control mean score at 12 weeks (9.3 *vs* 9.5)	-
				Intrusion errors intervention *vs* control at 12 weeks (0.98 *vs* 2.3), F (1, 23) = 3.35, Cohen's f = 0.35)	-
			CVLT Recognition Memory	Intervention *vs* Control mean score at 12 weeks (14.4 *vs* 14.2)	-
				Intrusion errors intervention *vs* control at 12 weeks (0.88 *vs* 2.2), F (1, 23) = 2.94, Cohen's f = 0.34)	-
	Desideri et al., 2012[34]	990 mg HF *vs* IF *vs* LF cocoa flavanols per day	Verbal Fluency	HF (mean change +8.0 (SD+-5.3) words per 60 seconds**); IF (mean change +5.1 (SD+-3.1) words per 60 seconds**), LF (mean change +1.2 (SD+-2.7) words per 60 seconds*)	✓
	Bo et al., 2017[28]	480mg of DHA + 720mg of EPA daily *vs* placebo	Working memory	Intervention mean difference 3.32 (SD ±3.45); Control mean difference 1.38 (SD ±2.66)	✓
			Recognition memory	Intervention: mean change 1.55 (SD ±3.96); Control mean change 1.98 (SD ±3.13)	-

RAVLT, Rey Auditory Verbal Learning Test; SD, Standard Deviation; HVLT-R, Hopkins Verbal Learning Test – Revised; tHcy, Total Homocysteine; GI, Glycaemic Index; aMCI, amnesic Mild Cognitive Impairment; SEM, Standard Error of the Mean; VPAL, Verbal Paired Associates Learning; CVLT, California Verbal Learning Test; CrPic, Chromium Picolinate; CDT, Clock Drawing Test; NTB, Neuropsychological Test Battery; *Statistically significant difference p≤0.05 within group; **Statistically significant difference p≤0.001 within group; ✓Statistically significant difference (p≤0.05) between intervention & control groups at study completion; - No statistically significant difference between intervention & control at study completion; † Statistically significant difference between intervention & control at stated time-point

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NIA-AA Cognitive Domain	Study	Intervention	Cognitive Function Measure used	Intervention group and Control Group Results	Between Group Difference
	Soininen et al., 2017[33]	Souvenaid, a 125ml once-a-day drink *vs* control	NTB Memory Z score	Intervention mean change at 24 months, 0.003 (SD 0.569); Control mean change at 24 months -0.130 (SD 0.619)	-
	Zhang et al., 2017[30]	2g/day DHA *vs* placebo	Information Test	Intervention mean score 12.28 (SD ±3.56); Control mean score 10.82 (SD±2.62)	✓
			Digit Span	Intervention mean score 13.44 (SD±3.66); Control mean score 10.25 (SD±3.42)	✓
	Phillips et al., 2015[29]	625mg EPA +600mg DHA *vs* placebo	Immediate Verbal Memory	Intervention mean score (month 1, 19.42 (SD 3.49) -month 4, 17.46 (SD 4.52)); Control mean score (month 1, 20.50 (SD 4.31) - month 4, 19.38 (SD 4.65))	-
			Delayed Verbal Memory	Intervention mean score (month 1, 4.85 (SD 2.91) -month 4, 4.34 (SD 2.74)); Control mean score (month 1, 5.23 (SD 2.63) -month 4, 4.65 (SD 2.79))	-
			Recognition Verbal Memory	Intervention mean score (month 1, 8.92 (SD 2.06) -month 4, 8.38 (SD 2.30)); Control mean score (month 1, 9.00 (SD 2.80) -month 4, 8.00 (SD 2.55))	-
			Visual Memory	Intervention mean score (month 1, 11.58 (SD 2.19) -month 4, 12.77 (SD 2.67); Control mean score (month 1, 11.50 (SD 2.60) -month 4, 11.85 (SD 1.95))	-
Executive Function	Lee et al., 2013[27]	Fish oil supplementation with concentrated DHA+EPA *vs* placebo	Digit Symbol Substitution	Intervention (baseline mean score 5.5, 95% CI 3.723–7.218 – 12 months mean score 5.5, 95% CI 3.723–7.218); Control (baseline mean score 4.9, 95% CI 3.254–6.634 – 12 months mean score 4.9, 95% CI 3.254–6.634)	-
			Clock Drawing Test (CDT)	Intervention (baseline mean score 7.3, 95% CI 6.810–7.880 – 12 months mean score 7.8, 95% CI 7.142–8.477); Control (baseline mean score 7.5, 95% CI 6.935–7.969 – 12 months mean score 7.8, 95% CI 7.145–8.436)	-
			Executive Function Z Score (cumulative score of all tests used)	Intervention (mean change 0.52 (SD 0.869)*); Control (mean change −0.238 (0.683))	-
	Petersen et al., 2005[31]	2000 IU vit E, 10 mg donepezil or placebo	Executive Function Z score (Digits backwards test, Symbol digit modalities test & Number - cancellation test)	Intervention (6 months Z score 0.11, SD±0.41† – 36 months Z score -0.19, SD±0.48); Control (6 months Z score 0.04, SD±0.42 – 36 months Z score -0.19 SD±0.53)	-

RAVLT, Rey Auditory Verbal Learning Test; SD, Standard Deviation; HVLT-R, Hopkins Verbal Learning Test – Revised; tHcy, Total Homocysteine; GI, Glycaemic Index; aMCI, amnesic Mild Cognitive Impairment; SEM, Standard Error of the Mean; VPAL, Verbal Paired Associates Learning; CVLT, California Verbal Learning Test; CrPic, Chromium Picolinate; CDT, Clock Drawing Test; NTB, Neuropsychological Test Battery; *Statistically significant difference p≤0.05 within group; **Statistically significant difference p≤0.001 within group; ✓Statistically significant difference (p≤0.05) between intervention & control groups at study completion; - No statistically significant difference between intervention & control at study completion; † Statistically significant difference between intervention & control at stated time-point

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NIA-AA Cognitive Domain	Study	Intervention	Cognitive Function Measure used	Intervention group and Control Group Results	Between Group Difference
	Horie et al., 2016[37]	Nutrition counselling & calorie restriction *vs* standard care	Trail making test, part B	Intervention (mean change -8.6, 95% CI -71.6±54.5); Control (mean change 5.1, 95% CI -58.3±68.6)	-
			Phonemic fluency	Intervention (mean change 0.1, 95% CI -0.5±5.1); Control (mean change 2.0, 95% CI -3.1±7.1)	-
			Semantic Fluency	Intervention (mean change 1.1, 95% CI -1.4±3.6); Control (mean change 1.9, 95% CI -0.6±4.4)	-
			Modified Wisconsin Card Sorting Test	Intervention (mean change 0.4, 95% CI -0.3±1.0); Control (mean change 0.7, 95% CI -0.1±1.4)	-
	Krikorian et al., 2012[12]	High carbohydrate diet *vs* very low carbohydrate	Trail making test, part B	Intervention (pre-intervention mean score 79.2 seconds *vs* post intervention mean score 82.9 seconds, F(1, 20) = 0.46); Control (no detail)	-
	Bayer-Carter et al., 2011 [38]	High fat/high GI diet *vs* Low fat/ low GI diet	Trail making test, part B Stroop colour word test Verbal fluency	*The authors did not include these data in their published paper, merely stating no diet related changes in the text*	-
	De Jager et al., 2012[25]	0.8mg folic acid, 0.5mg vitamin B12 and 20mg vitamin B6 *vs* placebo	CLOX (subgroup analyses, with baseline tHcy levels)	The odds of a correctly drawn item from CLOX1, after controlling for confounders (CLOX2 at follow-up, CLOX1 at baseline, age, education, APOE Ɛ4 status and sex), was 30% greater in those receiving B-vitamins in comparison to placebo (OR= 0.26)	✓
	Desideri et al., 2012[34]	990 mg HF *vs* IF *vs* LF cocoa flavanols per day	Trail making test, part B	HF (mean change -29.2 (SD ±8.0) seconds**), IF (mean change -22.8 (SD±5.1) seconds**) LF (mean change +3.8 (SD±16.3) seconds)	✓
	Soininen et al., 2017[33]	Souvenaid, a 125ml once-a-day drink *vs* control	NTB Executive Function Z score	Intervention mean change at 24 months -0.145 (SD 0.445); Control mean change at 24 months -0.039 (SD 0.506)	-
	Phillips et al., 2015[29]	625mg EPA +600mg DHA *vs* placebo	CLOX2	Intervention mean score (month 1, 14.08 (SD 0.89)-month 4, 14.08 (SD 14.08)); Control mean score (month 1, 14.38 (SD 0.75)-month 4, 14.27 (SD 0.67))	-

RAVLT, Rey Auditory Verbal Learning Test; SD, Standard Deviation; HVLT-R, Hopkins Verbal Learning Test – Revised; tHcy, Total Homocysteine; GI, Glycaemic Index; aMCI, amnesic Mild Cognitive Impairment; SEM, Standard Error of the Mean; VPAL, Verbal Paired Associates Learning; CVLT, California Verbal Learning Test; CrPic, Chromium Picolinate; CDT, Clock Drawing Test; NTB, Neuropsychological Test Battery; *Statistically significant difference p≤0.05 within group; **Statistically significant difference p≤0.001 within group; ✓Statistically significant difference (p≤0.05) between intervention & control groups at study completion; - No statistically significant difference between intervention & control at study completion; † Statistically significant difference between intervention & control at stated time-point

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NIA-AA Cognitive Domain	Study	Intervention	Cognitive Function Measure used	Intervention group and Control Group Results	Between Group Difference
Attention	Horie et al., 2016[37]	Nutrition counselling & calorie restriction *vs* standard care	Digit span forward	Intervention (mean change -0.4, 95% CI -1.1±0.3); Control (mean change 0.1, 95% CI -0.6±0.9)	-
			Digit span backward	Intervention (mean change 0.2, 95% CI -0.8±1.2); Control (mean change 0.1, 95% CI -0.9±1.1)	-
			Trail making test, part A	Intervention (mean change -6.1 95% CI -22.6±10.4); Control (mean change -0.7, 95% CI -17.3±15.9)	-
	Lee et al., 2013[27]	Fish oil supplementation with concentrated DHA+EPA *vs* placebo	CDT	Intervention (baseline mean score 7.3, 95% CI 6.810–7.880 – 12 months mean score 7.8, 95% CI 7.142–8.477); Control (baseline mean score 7.5, 95% CI 6.935–7.969 – 12 months mean score 7.8, 95% CI 7.145–8.436)	-
			Digit span forward test	Intervention (baseline mean score 8.0, 95% CI 6.99 –9.04 – 12 months mean score 9.6, 95% CI 8.437–10.749); Control (baseline mean score 8.5, 95% CI 7.554–9.529 – 12 months mean score 8.0, 95% CI 6.877–9.113)	✓
			Attention Z Score	Intervention (mean change 0.52 (SD 0.869)*); Control (mean change −0.238 (0.683))	-
	Desideri et al., 2012[34]	990 mg HF *vs* IF *vs* LF cocoa flavanols per day	Trail making test, part A	HF (mean change -14.3 (SD±4.2) seconds**), IF (mean change -8.8 (SD±3.4) seconds**), LF (mean change +1.1 (SD±13.0) seconds)	✓
	Zhang et al., 2017[30]	2g/day DHA *vs* placebo	Digit span	Intervention mean score 13.44 (SD±3.66); Control mean score 10.25 (SD±3.42)	✓
	Philips et al., 2015[29]	625mg EPA +600mg DHA *vs* placebo	Basic Attention	Intervention mean score (month 1, 6.38 (SD 1.47) - month 4, 6.54 (SD 1.33); Control mean score (month 1, 6.65 (1.36) - month 4, 6.77 (SD 1.31))	-

RAVLT, Rey Auditory Verbal Learning Test; SD, Standard Deviation; HVLT-R, Hopkins Verbal Learning Test – Revised; tHcy, Total Homocysteine; GI, Glycaemic Index; aMCI, amnesic Mild Cognitive Impairment; SEM, Standard Error of the Mean; VPAL, Verbal Paired Associates Learning; CVLT, California Verbal Learning Test; CrPic, Chromium Picolinate; CDT, Clock Drawing Test; NTB, Neuropsychological Test Battery; *Statistically significant difference p≤0.05 within group; **Statistically significant difference p≤0.001 within group; ✓Statistically significant difference (p≤0.05) between intervention & control groups at study completion; - No statistically significant difference between intervention & control at study completion; † Statistically significant difference between intervention & control at stated time-point

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NIA-AA Cognitive Domain	Study	Intervention	Cognitive Function Measure used	Intervention group and Control Group Results	Between Group Difference
Language	Horie et al., 2016[37]	Nutrition counselling & calorie restriction *vs* standard care	Semantic fluency	Intervention (mean change 1.1, 95% CI -1.4±3.6); Control (mean change 1.9, 95% CI -0.6±4.4)	-
			Phonemic fluency	Intervention (mean change 0.1, 95% CI -0.5±5.1); Control (mean change 2.0, 95% CI -3.1±7.1)	-
	Petersen et al., 2005[31]	2000 IU vit E, 10 mg donepezil, or placebo	Language Z Score (Boston naming test & Category fluency test)	Intervention (6 months Z score 0.07, SD±0.23† – 36 months Z score -0.10, SD±0.35); Control (6 months Z score 0.03, SD±0.23 – 36 months -0.08, SD±0.33)	-
Visuo-spatial Skills (VS)	Lee et al., 2013[27]	Fish oil supplementation with concentrated DHA+EPA *vs* placebo	Matrix reasoning block design test	Intervention (baseline mean score 7.6, 95% CI 6.37–8.75 – 12 months mean score 7.1, 95% CI 6.27–7.96); Control (baseline mean score 7.3, 95% CI 6.16–8.45 – 12 months mean score 7.9, 95% CI 7.07–8.71)	-
			VS Z score	Intervention (mean change 0.17 (SD 0.84)); Control (mean change 0.04 (SD 0.60))	-
	Petersen et al., 2005[31]	2000 IU vit E, 10 mg donepezil, or placebo	VS Z score (CDT)	Intervention (6 month Z score 0.03, SD± 0.34 – 36 months Z score -0.12, SD±0.37); Control (6 month Z score -0.01, SD±0.34 – 36 months Z score -0.11, SD±0.39)	-
	Ma et al., 2016[24]	folic acid (400µg/day) *vs* control	Block design test	Intervention (baseline mean score 9.77 (SD±5.41) – 6 months mean score 13.28 (SD±4.21)); Control (baseline mean score 9.93 (SD±2.273)- 6 months mean score 11.33 (SD±3.11))	✓
	Zhang et al., 2017[30]	2mg DHA *vs* placebo	Block design test	Intervention (baseline mean score 10.25 (SD±5.30 – 12 months mean score 11.19 (SD±4.07); Control (baseline mean score 9.63 (SD±2.46 – 12 months mean score 10.43 (SD±3.51))	-

RAVLT, Rey Auditory Verbal Learning Test; SD, Standard Deviation; HVLT-R, Hopkins Verbal Learning Test – Revised; tHcy, Total Homocysteine; GI, Glycaemic Index; aMCI, amnesic Mild Cognitive Impairment; SEM, Standard Error of the Mean; VPAL, Verbal Paired Associates Learning; CVLT, California Verbal Learning Test; CrPic, Chromium Picolinate; CDT, Clock Drawing Test; NTB, Neuropsychological Test Battery; *Statistically significant difference p≤0.05 within group; **Statistically significant difference p≤0.001 within group; ✓Statistically significant difference (p≤0.05) between intervention & control groups at study completion; - No statistically significant difference between intervention & control at study completion; † Statistically significant difference between intervention & control at stated time-point